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ORIGINAL PAPER

# Adaptation of the Skeletal System During Long-Duration Spaceflight

**Jean D. Sibonga · Peter R. Cavanagh · Thomas F. Lang · Adrian D. LeBlanc · Victor S. Schneider · Linda C. Shackelford · Scott M. Smith · Laurence Vico**



**Abstract** This review will highlight evidence from crew members flown on space missions >90 days to suggest that the adaptations of the skeletal system to mechanical unloading may predispose crew members to an accelerated onset of osteoporosis after return to Earth. By definition, osteoporosis is a skeletal disorder—characterized by low bone mineral density (BMD) and structural deterioration—that reduces the ability of bones to resist fracture under the loading of normal daily activities. "Involutional" or age-related osteoporosis is readily recognized as a syndrome afflicting the elderly population because of the insipid and asymptomatic nature of bone loss that does not typically manifest as fractures until after age ~60. It is not the thesis of this review to suggest that spaceflight-induced bone loss is similar to bone loss induced by metabolic bone disease; rather this review draws parallels between the rapid and earlier loss in females that occurs with menopause and the rapid bone loss in middle-aged crew members that occurs with spaceflight unloading and how the cumulative effects of spaceflight and ageing could be detrimental, particularly if skeletal effects are totally or partially irreversible. In brief, this report will provide detailed evidence that long-duration crew members, exposed to the weightlessness of space for the typical long-duration (4–6 months) mission on Mir or the International Space Station, (1) display bone resorption that is aggressive, that targets normally weight-bearing skeletal sites, that is uncoupled to bone formation, and that results in areal BMD deficits that can range between 6 and 20% of preflight BMD; (2) display compartment-specific declines in volumetric BMD in the proximal femur (a skeletal site of clinical interest) that significantly reduces its compressive and bending strength and may account for the loss in hip bone strength (i.e., force to failure); (3) recover BMD over a post-flight time period that exceeds spaceflight exposure but for which the restoration of whole bone strength remains an open issue and may involve structural alteration; and (4) display risk factors for bone loss—such as the negative calcium balance and down-regulated calcium-regulating hormones in response to bone atrophy—that can be compounded by the constraints of conducting mission operations (inability to provide essential nutrients and vitamins). The full characterization of the skeletal response to mechanical unloading in space is not complete. In particular, countermeasures used to date have been inadequate, and it is not yet known whether more appropriate countermeasures can prevent the changes in bone that have been found in previous flights. Knowledge gaps related to the effects of prolonged (≥6 months) space exposure and to partial gravity

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environments are substantial, and longitudinal measurements on crew members after spaceflight are required to assess the full impact on skeletal recovery.

**Keywords** Bone · Mechanical unloading · Weightlessness · Bed rest · Astronauts · Cosmonauts

**Abbreviations**

| | |
|---|---|
| BMD | Bone mineral density |
| DXA | Dual-energy X-ray absorptiometry |
| FEA | Finite element analysis |
| ISS | International Space Station |
| MRI | Magnetic resonance imaging |
| PTH | Parathyroid hormone |
| QCT | Quantitative computed tomography |
| UV | Ultraviolet |
| WHO | World Health Organization |

## Introduction

Early in the space program, it was recognized that immobilization in those first spacecrafts for manned missions, coupled with the gravitational unloading, could have detrimental effects on calcium metabolism. The impetus behind the next 40+ years of bone research in space may have come in the 1940s when the premier endocrinologist, Fuller Albright, called attention to the disturbed calcium metabolism evident in a young patient experiencing prolonged bed rest [1]. This was subsequently proven by Whedon and colleagues in studies demonstrating that musculoskeletal atrophy was due to the mechanical unloading of prolonged bed rest and not disease per se [2]. Consequently, seminal investigations and evaluations of the skeletal system were initiated with the Gemini flights, as best as could be achieved given the constraints of operating a spaceflight mission and the available technology in the early 1960s. As technology has advanced, so has the characterization of skeletal adaptation to weightlessness. As outlined in Fig. 1, the database for the skeletal effects of spaceflight was expanded along with the technologies and analyses available during a spacecraft era.

To this day, the characterization of skeletal adaptation to space (termed "space normal" by the NASA Human Research Program at Johnson Space Center) is paramount as NASA prepares to embark on exploration class missions with a return to the moon and human exploration of other planetary surfaces. Understanding the physiological effects of spaceflight is critical as NASA identifies the health risks associated with these longer-duration flights and develops appropriate countermeasures to eliminate or mitigate these effects. While the current understanding of "space normal" for bone has been limited by the number of crew members and flight opportunities, the current database on the skeletal adaptation to space provides sufficient evidence to document that prolonged exposure to the space environment without appropriate countermeasures compromises the skeleton and may increase the risk for fractures at an earlier age.

In order to understand how the adaptive response to space predisposes crew members to early onset osteoporosis, it is important to appreciate how space exposure impacts the multiple facets of skeletal remodeling and how those changes in crew members (predominantly driven by biomechanics) relate to terrestrial changes in the ageing human (predominantly driven by metabolic pathologies).

## Background

Osteoporosis is a skeletal disease characterized by several features of a deteriorated skeleton that collectively compromise whole bone strength and increase the propensity for fracture in afflicted individuals. This syndrome can be a consequence of the *ageing* process [3, 4] which begins during late puberty following the closure of epiphyseal growth plates. However, the sex-specific effects of growth also influence age-related bone loss since estrogen suppression of radial and longitudinal bone growth in females, with the onset of puberty, results in smaller bones and less peak bone mass compared to their male counterparts. Later, with the onset of menopause, estrogen-deficient females experience an earlier, more rapid, phase of involutional bone loss which increases the incidence and prevalence of fractures in ageing women [3–5]. Likewise, it is widely acknowledged that osteoporosis can be induced by secondary factors, such as chronic use of glucocorticoid medication, alcoholism or decreased physical activity, where the suppressive effects on bone formation unbalance the remodeling process to favor net bone loss. Thus, osteoporosis has multiple pathophysiologies that can have additive effects.

After more than 40 years of human spaceflight, the mechanical unloading of space is a well-recognized risk factor for bone loss [6]. Whether it is a factor for secondary osteoporosis in crew members is dependent upon the length of time the skeleton is unloaded in space and whether it can be restored to its previous pre-launch state upon return to normal mechanical loading of Earth. If the skeletal decrements during space travel are irreversible, even if osteoporosis is not diagnosed at landing, the result may be an earlier diagnosis in the crew member's life compared to the expected temporal onset with age-related bone loss. Understanding the skeletal response to the mechanical unloading of spaceflight starts with understanding how the adult skeleton undergoes bone turnover through the highly

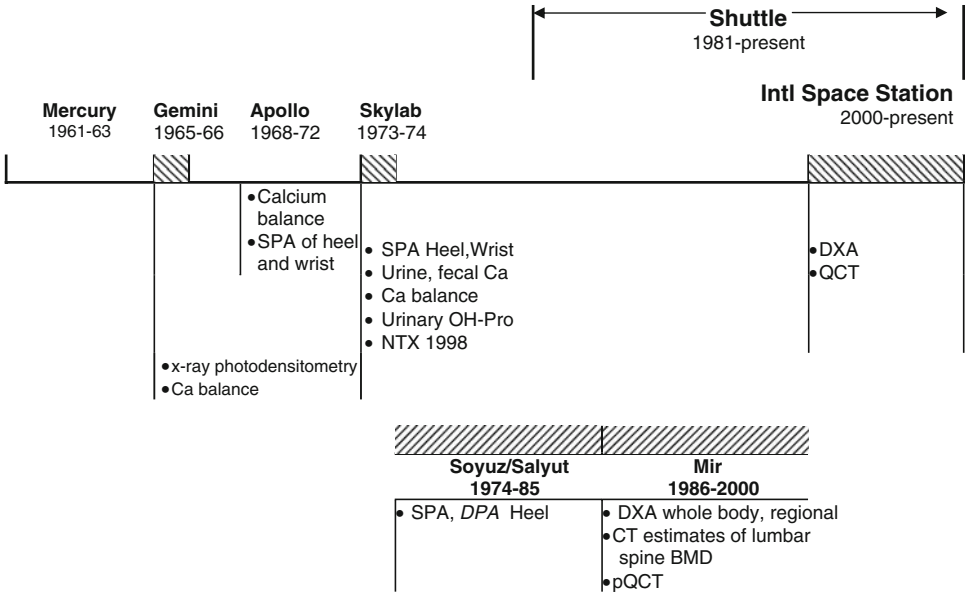



**Fig. 1** History of early measures in space program. Ca, calcium; SPA, single photon absorptiometry; OH-Pro, hydroxyproline; NTX, N-telopeptide; DXA, dual-energy X-ray absorptiometry; pQCT, peripheral quantitative computed tomography; DPA, dual photon absorptiometry; CT, computed tomography; and BMD, bone mineral density

mediated process of bone remodeling in a standard gravitational field.

On Earth, the adult human skeleton renews and repairs itself with approximately one tenth of the skeleton renewed on an annual basis. In response to putative osteocytic cell signaling, skeletal remodeling is initiated in discrete packets of skeletal tissue referred to as "bone remodeling units" where the removal and replacement of bone tissue is the result of a well-orchestrated action of bone resorbing (hematopoietic stem cell-derived osteoclasts) and bone forming cells (stromal cell-derived osteoblasts). This cellular regulation ensures: (i) the temporal formation of bone after the resorption of bone (i.e., "bone coupling") and (ii) the spatial formation of a bone volume to replace the resorbed volume in the resorption pits or lacunae ("bone balance"). Any perturbation to this cellular process, e.g., induced by endocrine or nutritional deficiencies or by changes in mechanical stresses, can disrupt this balance in the bone remodeling unit resulting in a deficit of bone, a gain of bone, or a change in material properties of bone. With 1–2 million bone remodeling units in the adult skeleton [7], a negative balance of bone in each unit can reduce skeletal mass over time and compromise the skeleton's integrity under normal mechanical loading.

When remodeling is accelerated, as with menopausal bone loss, the "birth rate" of bone remodeling units is high. This acceleration can be quantified by histomorphometry with the index of Activation Frequency, which has been shown to increase in the ageing female (Fig. 2) [8]. Histomorphometric analyses have further revealed how increased numbers of bone remodeling units can perforate horizontal trabecular struts of cancellous bone microarchitecture and induce greater porosity in cortical bone. The loss of trabecular elements and of connectivity between trabeculae

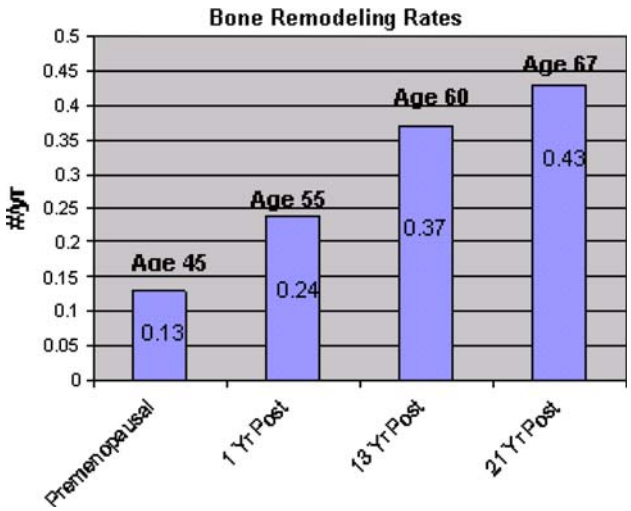



**Fig. 2** Increases in activation frequency in females as a function of menopausal status and the number of years following menopause onset. Activation frequency (expressed in year$^{-1}$) is calculated from histomorphometric indices of bone remodeling and serves as a measure of bone turnover. Adapted figure from Ref. [8]

reduces the mechanical strength of the trabecular scaffold. The accelerated loss of bone with menopause targets the cancellous bone compartment (i.e., trabecular or spongy bone) where resorption preferentially occurs along the bone surfaces adjacent to bone marrow. This mechanism of bone loss leads to: (i) thinning of the cortical bone shell and the trabecular plates, (ii) perforation of trabecular struts, and (iii) loss of trabecular elements and connectivity [5, 9, 10]. With menopause, there is a 20–30% reduction in *cancellous* bone compared to the 5–10% losses of cortical bone associated with the first decade after menopause and accounting for a higher incidence of fractures in women (compared to men of

same age range) at those skeletal sites predominantly composed of cancellous bone (wrist fractures and vertebral crush fractures) [3]. Increased remodeling, moreover, can also be inferred by increased levels of biomarkers for bone formation and bone resorption [11, 12].

More recently, the application of the more sensitive quantitative computed tomography (QCT) to a population study substantiated that there are earlier and persistent losses in cancellous bone in both men and women (~33 and 50% of total lifetime loss, respectively) [13, 14]. Likewise, substantial losses in cortical bone in women were initiated around mid-life with menopause onset while cortical bone loss in men did not accelerate until much later. Together with the observation that women have smaller bones from the outset, the deficiency of estrogen with menopause is a major contributing factor to osteoporosis (and its associated fragility fractures) in women compared to men at the same age.

The knowledge base underlying the spaceflight-induced bone loss is limited in comparison to what is known about the pathophysiology of primary osteoporosis or for the cellular mechanisms of secondary osteoporosis in the terrestrial populations. Spaceflight missions do not typically provide controllable experimental conditions for the systematic collection of data; experiments are restricted by power, mass, and volume requirements; flight opportunities are few and far between; and subjects for testing or for longitudinal measures are too few to obtain definitive answers. Even so, the limited data from spaceflight can be evaluated in the context of the extensive knowledge base for terrestrial osteoporosis.

Hence this review of spaceflight analyses will span the perturbations in calcium homeostasis and in bone remodeling that were detected with short durations of spaceflight (<90 days as defined herein, but typically <2–3 weeks based on mission durations) to the measurable decrements in bone mineral densities and in bone structure in "long-duration" crew members after spaceflight exposures of typically ~4–6 months. Also described is the computer modeling—based upon data from three-dimensional bone images—that has enabled estimations of hip bone strength immediately following long-duration missions. A summary of knowledge gaps will highlight work that remains to be done, with spaceflight and/or with ground-based analogs, to substantiate the risk for an earlier onset of osteoporosis in crew members after prolonged space missions.

## Human Spaceflight Data

### Evidence for Perturbed Bone Remodeling

There is evidence from bone turnover markers to suggest that the remodeling process is uncoupled in space leading to an unbalanced remodeling of bone and a deficit in bone mass. Indirect measures of turnover at the level of the entire skeleton indicate increased bone resorption, while bone formation appears to be unchanged or decreased. Early in the space program, biochemical assays of specimens collected in flight detected a greater excretion of collagen degradation products relative to circulating proteins/peptides that are synthesized and released by osteoblasts during bone formation. Increased bone resorption was evident with the elevated excretion of hydroxyproline relative to preflight level detected in all three Skylab missions [15]; this finding was corroborated almost two decades later when archived urine specimens were analyzed by state-of-the-art assays for cross-linked collagen fragments (e.g., N-telopeptide, NTX) [16]. Likewise, Smith et al. [17] documented how spaceflight increased NTX excretion, with minimal influence on circulating levels of the osteocalcin, as determined in flight specimens of Mir crews. This pattern supported the earlier evidence of suppressed circulation of procollagen type I C-terminal peptide, bone-specific alkaline phosphatase, and osteocalcin (i.e., formation markers), concurrent with increased excretion of bone resorption markers in the Mir crew members [18]. Furthermore, measurement of C-telopeptide (CTX) in both urine and serum in the two Mir cosmonauts indicated a greater concentration in serum as early as 8 days into the flight. An increase in undercarboxylated bone gla protein (i.e., osteocalcin) was evident, suggesting an impairment of vitamin K metabolism, the origins of which remain to be further investigated [19]. Collectively, these systemic indices of bone turnover suggest that mechanical unloading uncouples bone remodeling and, due to the "aggressive" action of osteoclasts, the resorbed volume of bone exceeds the volume of bone formed by osteoblasts.

### Presence of Additional Risk Factors for Bone Loss

Bone loss in space reflects alterations in many processes. There are several risk factors present in crew members during and immediately after spaceflight, some of which may contribute to or may be a consequence of the bone loss induced by spaceflight. Mineral metabolic studies that were conducted during the 28-, 56-, and 84-day Skylab missions enabled Whedon and colleagues to characterize the negative calcium (and mineral) balance with spaceflight [20–22]. Despite the large variability in the results, collectively the data suggested that skeletal deconditioning increased with longer mission durations [23]. There was a rapid and sustained elevation in urine calcium, a gradual increase in fecal calcium, and a negative calcium balance averaging approximately 7.5 g/month. These changes were accompanied by increased excretion of hydroxyproline and

hydroxylysine (early biomarkers of bone resorption), gradual decreases in intestinal calcium absorption, minor increases in plasma calcium and phosphorus, and a delayed (>4 weeks) reduction in serum parathyroid hormone (PTH). The data suggested that the negative calcium balance was likely due to bone atrophy (increased excretion) and to calcium malabsorption (decreased intake).

Measurements of calcium-regulating hormones in Mir crews showed trends for reduced PTH and 1,25-dihydroxy vitamin D concurrent with signs of increased bone resorption during spaceflight [17, 24]; the lack of statistical significance was likely a consequence of small subject numbers. These flight data further documented how increased atrophy of bone mildly increases serum calcium and phosphorus, leading to the reductions in calcium-regulating hormones and the poor conservation of calcium, and contributing to the negative calcium balance observed with spaceflight [17, 25].

## Changes in Bone Mass, Bone Mineral Density, and Bone Structure

Evaluations of bone density following prolonged space exposure were initially implemented with the three-manned crew of the Skylab missions and thus first demonstrated the regional specificity of bone loss in space. Measurements by single photon absorptiometry failed to show any impact of spaceflight on measurements in the upper body (wrist), but detected significant losses in the lower extremity (calcaneus, in 3 of 9 astronauts) [26]. Bone mineral density (BMD) changes in crews of different missions became more negative with increasing duration of Skylab flights (28, 56, and 84 days) (Fig. 3) [15]. Similarly, Oganov et al. [27] analyzed spine BMD with early application of computed tomography (CT). Evidence from four Russian cosmonauts, after 5–7 month space missions, similarly displayed large variability with losses in vertebral BMD in three cosmonauts (0.3–10.8%) and a gain of 2.3% in one cosmonaut [27].

It was with the advent of dual-energy X-ray absorptiometry (DXA) technology that the measurements of areal BMD showed changes that suggested accelerated bone turnover at skeletal sites that were normally weight-bearing on Earth. LeBlanc et al. [28] conducted DXA BMD measurements of crew members ($n = 16$–18) before and after serving on the Mir spacecraft (~4 months duration) to report a BMD change over an entire mission. However, because of the wide range of mission durations (~4–14 months) during this data-collection period, BMD losses were normalized to total months in space to report an averaged monthly loss of 1–1.5% (Table 1). Further assessment revealed large variability in BMD losses amongst crew members, both intraskeletally and interskeletally, and that the BMD losses were greater in the lower limbs and at weight-bearing sites of the central skeleton. These sites included the hip and spine, sites which have a high incidence of osteoporosis fractures in the elderly population on Earth. Based upon these flight data, and the precision evaluation for the densitometry machines, DXA measurement of BMD is applied only to crew members serving on spaceflight missions >30 days.

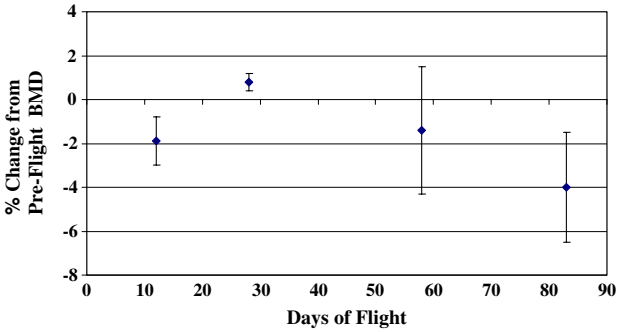



**Fig. 3** Early determination of changes in calcaneal BMD with spaceflight. BMD (mean ± SE) measured in 3-man crews serving on Skylab missions of varying durations and compared to measurements conducted in crew of 14-day missions (Apollo 14, 15, and 16). Adapted figure from Ref. [15] (Figure 3 is reprinted from cited references with permission from Elsevier Limited)

The averaged 1–1.5% monthly loss in BMD in crew members is truly accelerated compared to the 2–3% loss per year observed in postmenopausal females during what is characterized as the rapid bone loss phase the first decade after menopause onset [3]. Additionally, Fig. 4a, b provides a comparison of longitudinal changes in total hip BMD as a function of age for both men and women as reported by Warming et al. [29]; overlaid on the bar graph are data derived from crew members who served on missions on the International Space Station (ISS) and the Russian Mir spacecraft.

These population changes were measured over 2 years and compared to averaged BMD changes in long-duration

**Table 1** Change in BMD (averaged change per month) compared to pre-flight measurement in crew members serving on missions on the Mir spacecraft [28]

| BMD and body composition after 4–14.4 months of space flight | | | |
|---|---|---|---|
| Variable | *N* | %/month change | SD |
| BMD lumbar spine | 18 | −1.06* | 0.63 |
| BMD femoral neck | 18 | −1.15* | 0.84 |
| BMD trochanter | 18 | −1.56* | 0.99 |
| BMD total body | 17 | −0.35* | 0.25 |
| BMD pelvis | 17 | −1.35* | 0.54 |
| BMD arm | 17 | −0.04 | 0.88 |
| BMD leg | 16 | −0.34* | 0.33 |

* $P < 0.01$

crew members over the typical 6-month mission. For hip BMD, crew members in the age range 35–55 display a ~6-fold greater decrement after a 6-month spaceflight mission compared to the losses incurred over 24 months in men of comparable age. Comparisons of age-related losses in BMD were also conducted for the clinically relevant sites of forearm and spine where male crew members displayed large BMD variability in the lumbar spine and forearm (Fig. 4c, d), The losses quantified in the long-duration female crew members may be comparable to losses measured in the 50–59 population age group (Fig. 4e, f), but currently the number of subjects is small ($n = 3$).

## Reductions in Bone Volumetric Density, Size, and Structure

There is evidence that indicates a differential loss of mineral mass in bone compartments. A preferential BMD loss in cancellous versus cortical bone compartments (on basis of percentage) has been detected in both Russian and US crew serving in long-duration (>30-day to 6-month missions) as determined by peripheral QCT and QCT technology [30, 31]. In particular, QCT scans performed in the spine and the total hip (femoral neck and proximal femur) of crew members serving on 6-month missions on ISS quantified trabecular bone losses of 2.2–2.7% [31] of the hip and 0.7% of the lumbar spine as averaged to month of duration ($n = 14$ crew members) (Table 2). For the total hip and femoral neck, the percentage BMD loss was greater in the more metabolically active trabecular compartment, although the BMD loss, on a total mass basis, was greater in the highly dense, cortical bone due to loss from the endocortical surface [31]. There was no difference in compartment-specific changes in the integral versus trabecular bone compartments of the spine. These structural changes at the femoral neck imply a reduction in both estimated axial compressive strength and bending strength [31]. The reductions in *integral* volumetric BMDs [31], which measured combined volumetric BMDs of cortical and cancellous bone, highlighted the failure of an in-flight exercise program on the ISS to mitigate the BMD losses detected by DXA in the crew members of the earlier Mir spacecraft era [28].

## Response on Earth After Spaceflight

There is evidence that the recovery of space-induced bone loss is delayed in the post-flight period. Vico et al. [30] failed to detect any recovery of BMD in the lower limbs of crew members who had served 6 months in space. Measurement of BMD by peripheral QCT had been conducted soon after flight and repeated 6 months after landing, suggesting that if the skeleton recovered lost BMD it would occur on Earth after a period longer than the mission duration [30]. Additionally, Lang et al. [32] repeated QCT scans at the proximal femur in ISS crew members 1 year after landing where an increase in cross-sectional volume at the femoral neck, compared to the measurements soon after landing, was evident but with a persistent depression in volumetric BMD. These data at 1 year post-flight indicate that radial bone growth was stimulated upon return to Earth's gravitational field but that the increased volume remained under-mineralized. Furthermore, recovery of volumetric BMD in the trabecular bone compartment was not evident (Lang, unpublished data).

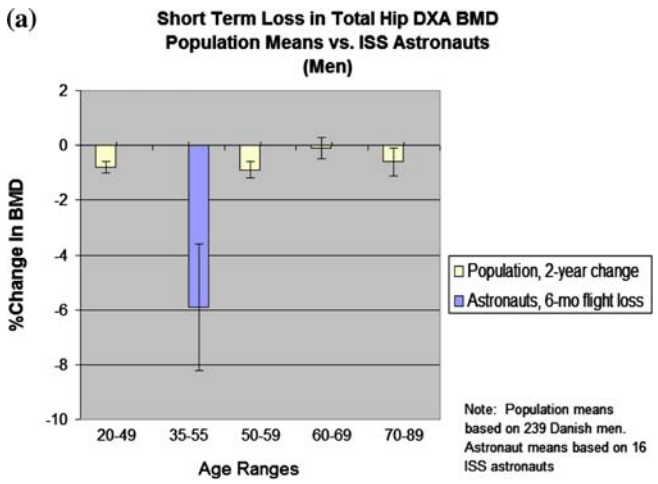
The spaceflight-induced geometrical changes at the femoral neck are similar to the adaptive response of periosteal osteoblasts to the cortical thinning and trabecular bone loss normally observed with age-related bone loss in the elderly [5, 10], suggesting a compensatory physiological response of the skeleton to recover compressive and bending strength. QCT analysis of age and sex differences in bone geometry [13] similarly documented apposition of bone at the periosteal surface in response to thinning of the cortex by age-related, net losses of bone at the endocortical surface.

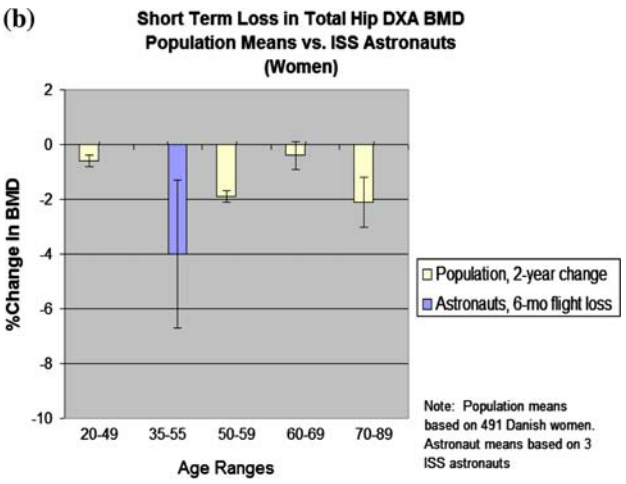
Recently, a novel method of analyzing areal BMD has been reported that characterizes post-flight skeletal recovery [33]. BMD measurements have been accumulated over a post-flight period lasting as long as 5 years. Data points from a repository of DXA BMD measurements (both cross sectional and longitudinal) of 45 different crew members serving on 56 different missions (4–14 months) were fitted to a two-parameter exponential mathematical equation (Fig. 5). The derivation of a "half-life" index provided a time point (days after landing) which represented the timing of 50% restoration of BMD. Table 3 summarizes the "half-lives" and the losses at the time of landing for the skeletal sites evaluated for recovery. In spite of the large variability in the BMD measurements, and the uncertainty in half-life values (generally 3–9 months dependent upon skeletal site), the asymptotic increase in BMD over the post-flight period was clearly apparent and provided the basis for substantial recovery at ~4 times the half-life [33].

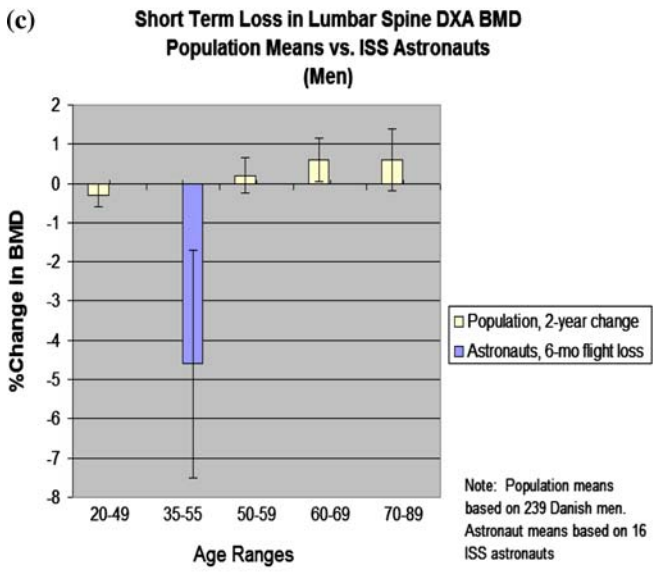
Furthermore, biochemical analyses of bone markers indicated that with return to Earth's gravity there was a reduced NTX excretion in urine, and there was a subsequent increase in serum levels of osteoblast-specific proteins (bone-specific alkaline phosphatase and osteocalcin) [17] (Fig. 6). This trend in biomarkers preceded the positive change in BMD, a pattern also observed in the reambulatory period following bed rest [34].

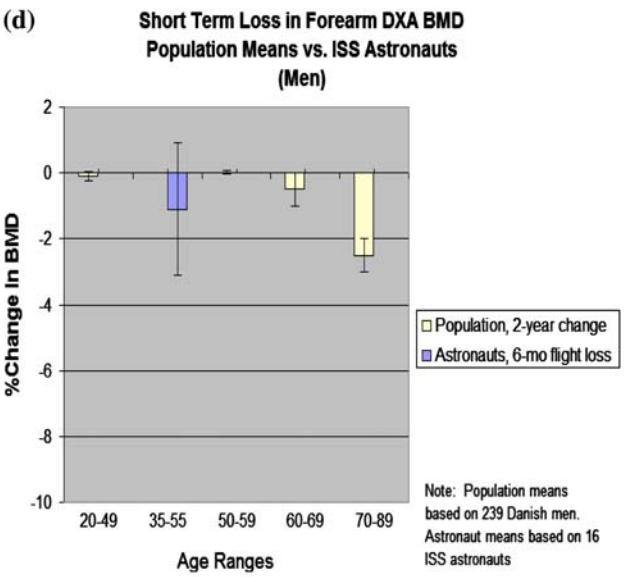
## Reductions in Whole Bone Strength

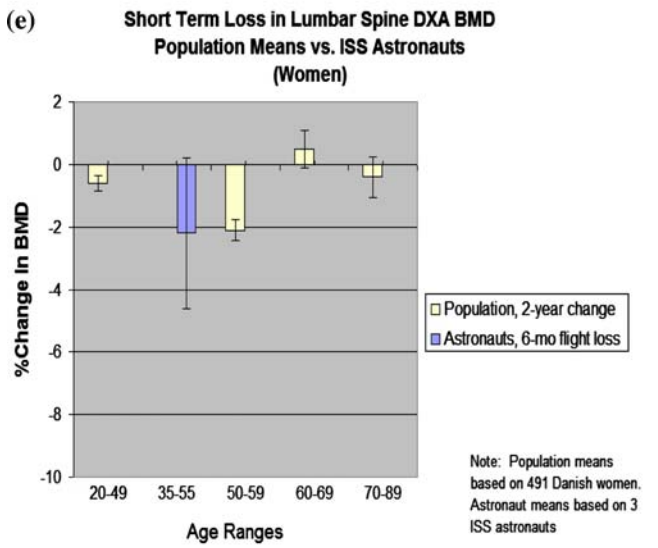
A finite element analysis (FEA) was developed from three-dimensional images of QCT hip scans to determine force to


(a)
Short Term Loss in Total Hip DXA BMD
Population Means vs. ISS Astronauts
(Men)
%Change In BMD
2
0
-2
-4
-6
-8
-10
20-49
35-55
50-59
60-69
70-89
Age Ranges
Population, 2-year change
Astronauts, 6-mo flight loss
Note: Population means based on 239 Danish men. Astronaut means based on 16 ISS astronauts


(b)
Short Term Loss in Total Hip DXA BMD
Population Means vs. ISS Astronauts
(Women)
%Change In BMD
2
0
-2
-4
-6
-8
-10
20-49
35-55
50-59
60-69
70-89
Age Ranges
Population, 2-year change
Astronauts, 6-mo flight loss
Note: Population means based on 491 Danish women. Astronaut means based on 3 ISS astronauts


(c)
Short Term Loss in Lumbar Spine DXA BMD
Population Means vs. ISS Astronauts
(Men)
%Change In BMD
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
20-49
35-55
50-59
60-69
70-89
Age Ranges
Population, 2-year change
Astronauts, 6-mo flight loss
Note: Population means based on 239 Danish men. Astronaut means based on 16 ISS astronauts


(d)
Short Term Loss in Forearm DXA BMD
Population Means vs. ISS Astronauts
(Men)
%Change In BMD
2
0
-2
-4
-6
-8
-10
20-49
35-55
50-59
60-69
70-89
Age Ranges
Population, 2-year change
Astronauts, 6-mo flight loss
Note: Population means based on 239 Danish men. Astronaut means based on 16 ISS astronauts


(e)
Short Term Loss in Lumbar Spine DXA BMD
Population Means vs. ISS Astronauts
(Women)
%Change In BMD
2
0
-2
-4
-6
-8
-10
20-49
35-55
50-59
60-69
70-89
Age Ranges
Population, 2-year change
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Note: Population means based on 491 Danish women. Astronaut means based on 3 ISS astronauts

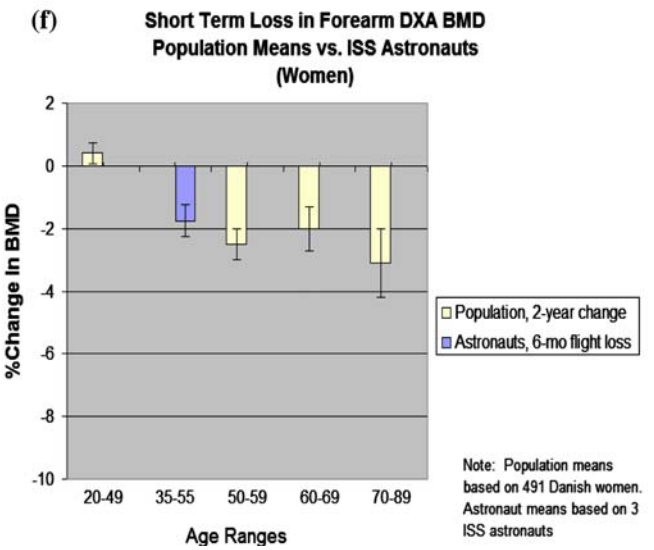
(f)
Short Term Loss in Forearm DXA BMD
Population Means vs. ISS Astronauts
(Women)
%Change In BMD
2
0
-2
-4
-6
-8
-10
20-49
35-55
50-59
60-69
70-89
Age Ranges
Population, 2-year change
Astronauts, 6-mo flight loss
Note: Population means based on 491 Danish women. Astronaut means based on 3 ISS astronauts

**Fig. 4** (**a**, **b**) (See figure on preceding page) Comparison of total hip BMD after spaceflight and in population. Changes in DXA-measured BMD male (**a**) and female (**b**) crew members serving on typical 6-month missions aboard the International Space Station. BMD change in space is compared to 2-year change in population of 239 Danish males (**a**) and 491 Danish females (**b**). Adapted figure from Ref. [29]. (**c**, **d**) Comparison of forearm and lumbar spine BMDs after spaceflight and in population. DXA-measured BMD change at the forearm (**c**) and lumbar spine (**d**) of male crew members serving on typical 6-month missions aboard the International Space Station compared to 2-year change in population of 239 Danish males. Adapted figure from Ref. [29]. (**e**, **f**) Comparison of forearm and lumbar spine BMDs after spaceflight and in population. Comparison of DXA-measured BMD change at the forearm (**c**) and lumbar spine (**d**) of female crew members serving on typical 6-month missions aboard the International Space Station compared to 2-year change in population of 491 Danish females. Adapted figure from Ref. [29] (Figure 4 is reprinted with permission from Springerlink.com)

**Table 2** Changes in volumetric BMD for combined cortical and cancellous bone compartments ("integral") and for trabecular bone compartment of the lumbar spine, total hip, and femoral neck

| QCT changes in volumetric BMD in 14 ISS crew members (% per month ± SD) | |
|---|---|
| Lumbar spine (integral) | −0.9 ± 0.5* |
| Lumbar spine (trabecular) | −1.7 ± 0.6* |
| Total hip (integral) | −1.4 ± 0.8* |
| Total hip (trabecular) | −2.3 ± 0.8* |
| Femoral neck (integral) | −1.2 ± 0.7* |
| Femoral neck (trabecular) | −2.7 ± 1.9* |

*Note*: Significant reductions from baseline (*$P < 0.05$) in volumetric BMD, expressed as loss averaged per month, for all sites with greater percentage deficit for trabecular bone of proxmal femur [31]

failure for loading of the femoral neck in two orientations: the posterior lateral direction (associated with backward falls to the side) and the axial direction (associated with stance) [35]. Keyak et al. applied this FEA to the QCT scans previously performed in crew members who served on the space station to determine compartmental bone effects [31, 36]. The FEA determined significant reductions in the estimated failure load (i.e., hip strength) after the 6-month mission relative to the determination made from pre-launch scans (Keyak, unpublished data).

The FEA was applied to QCT scans performed in five crew member subjects 1 year after returning, providing complete modeling at 3 time points (pre-flight, post-flight, and 1 year after return). There is a greater trend toward recovery of strength in stance loading (4/5 show minimal recovery in fall, 4/5 show strong recovery in stance) (Lang, personal communication). QCT, however, does not have the resolution for trabecular microarchitecture and consequently the FEA [35] may have underestimated the impact on hip bone strength. The same FEA was applied in a cross-sectional comparison of hip strength in young versus elderly

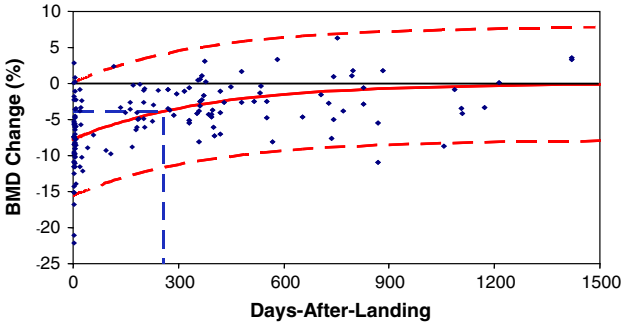


**Fig. 5** Recovery of BMD after landing as represented by data from the trochanter. Changes between pre- and post-flight BMD are plotted as a function of days after landing when the scans were performed. Data points are fitted to a two-parameter equation where the intercept of the fitted trochanter data identifies a spaceflight-induced bone loss of 7.8% of pre-flight BMD and a 50% recovery time for the loss to occur after about 8.5 months. Adapted figure from Ref. [33] (Figure 5 is reprinted from cited references with permission from Elsevier Limited)

**Table 3** Summary of fitted post-flight BMD data per skeletal site

| Skeletal site | Loss (L0) at landing (%) | 50% recovery time (days) |
|---|---|---|
| Femoral neck | 6.8 (5.7–7.9) | 211 (129–346) |
| Trochanter | 7.8 (6.8–8.8) | 255 (173–377) |
| Pelvis | 7.7 (6.5–8.9) | 97 (56–168) |
| Lumbar spine | 4.9 (3.8–6.0) | 151 (72–315) |
| Calcaneus | 2.9 (2.0–3.8) | 163 (67–395) |

*Note*: The percentage of pre-flight BMD loss at the time of landing and the 50% recovery time are listed per skeletal site, along with ranges. Fifty percent recovery time represents the number of days after landing at which time there is a restoration of half of the bone mineral that was lost during spaceflight. The L0 and recovery times were determined from fitted BMD data to 2-parameter exponential equation [33]

women [$n = 128$ (70–80 years) postmenopausal females versus $n = 30$ (35–45 years) pre-menopausal females] (Keyak, personal communication). This comparison suggested that the reduction in hip strength after 6 months of mechanical unloading by spaceflight was comparable to the lifetime reduction in hip strength (for fall loads) in an ageing female. And just as with the BMD losses during spaceflight at specific skeletal sites, the greater deficit in hip strength occurred at the site *within* the bone that adapts to weight-bearing while walking and standing on Earth.

## Evidence of Decreased Bone Formation

Mechanical unloading by spaceflight impairs the mineralization of bone. Histomorphometry of tetracycline-labeled iliac crest bone biopsies is the standard method for evaluating mineralization rates and mineralizing surfaces in skeletal tissue. However, no bone biopsies have been

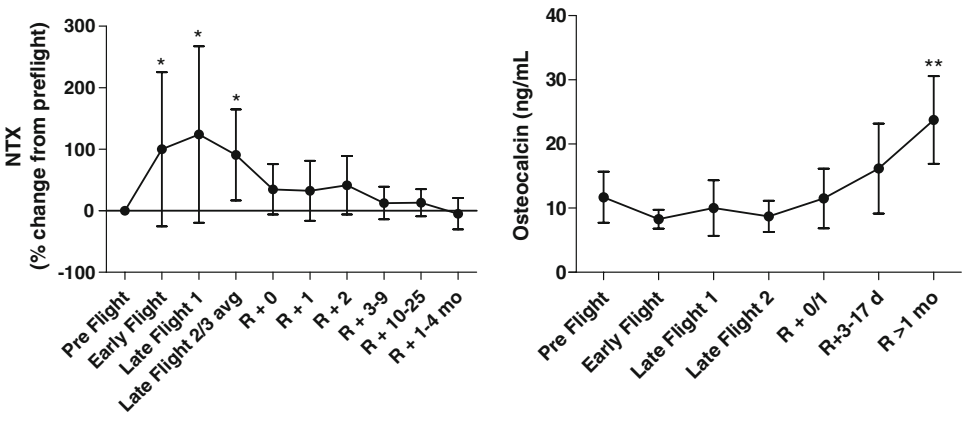


**Fig. 6** (**a**, **b**) Bone turnover markers measured in specimens collected pre-flight, during flight, and after flight suggest that return to Earth's 1 G environment reverses the increased excretion of bone resorption marker (*N*-telopeptide) and eventually stimulates expression of bone formation markers (e.g., osteocalcin). Adapted figure from Ref. [17]

obtained from a crew member before or after flight to assess the impact of spaceflight on either the production or the mineralization of matrix. Histomorphometry data, however, have been obtained from bone biopsies of non-human primates that were administered tetracycline prior to being flown in space [37, 38]. Compared to biopsies obtained pre-flight and from controls on the ground, there was a significantly reduced area of bone (with a tendency for thinner trabeculae) and reduced percentage of mineralizing surfaces in biopsies obtained post-flight. Histomorphometric changes were accompanied by a reduction in bone mineral content with flight.

## Ground-Based Analogs of Spaceflight Unloading of the Skeleton

Spaceflight analogs, both for human test subjects and animals, provide better controlled experimental conditions and opportunity for more extensive and invasive analytical methods to evaluate the effects of mechanical unloading. The following list highlights how these analogs are critical for corroborating and enhancing the limited spaceflight evidence base which is impacted by the constraints associated with mission operations: (a) mechanical unloading by bed rest down-regulates calcium regulating hormones [39, 40]; (b) mechanical unloading by prolonged bed rest appears to uncouple bone formation and bone resorption as reflected by changes in bone turnover markers [41, 42]; (c) mechanical unloading appears to uncouple osteoclastic (increases) and osteoblastic (decreases) mediation of bone remodeling as determined in bone biopsies [43–45]; (d) mechanical unloading, both by bed rest (120 days at the time point of biopsy) [46] and by spinal cord injury (2 years following injury) [47], results in a loss of connectivity in trabecular microarchitecture; and (e) mechanical unloading in non-human primates immobilized in a spaceflight analog impairs mineralization, accelerates bone resorption, and reduces bending strength [48–50]. These analyses of humans and non-human primates in ground-based models of mechanical unloading specifically detail the uncoupling of bone remodeling and the activity/number of bone cells. Delineating the impairment in turnover, at the cellular and tissue level, is critical for the selection of pharmaceutical countermeasures for the effects of skeletal adaptation in space.

More recently, the NASA Flight Analogs Project at the Johnson Space Center conducted a review of its recently initiated bed rest protocol to evaluate its validity as a standardized test bed for studies of mechanical unloading and as a critical research platform for the pre-flight evaluation of countermeasures to spaceflight-induced bone loss (and other physiological changes). DXA BMD measures in the first 13 test subjects are consistent with BMD changes documented in earlier bed rest and in spaceflight studies (Fig. 7), with statistically significant losses occurring in the hip, pelvis, and heel [51].

### Countermeasures Used to Date

The primary countermeasure for bone loss employed to date by both the US and Russian space programs has been exercise. The approaches used have been reviewed by a number of authors [52–56] and evidence suggests that none of the programs have been effective [28, 30, 31] in preventing skeletal changes.

A treadmill has always been a central component of the Russian countermeasures [53, 57] either as an exercise device or as a platform for static exercises [54]. Treadmills on the Russian space stations were fixed rigidly to the vehicle and were passive; that is there was no motor and the belt was driven by the exercising crew member. The load applied to the body during treadmill exercise in space depends critically on the "gravity replacement force" that is applied through a harness, and there are no published data to indicate the magnitude of forces that were used during Russian countermeasures. A cycle ergometer has also been used in the Russian program [52], as has a

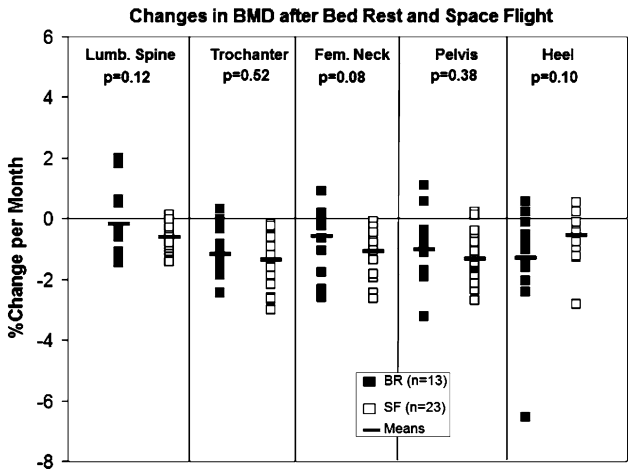


**Fig. 7** Changes in BMD after bed rest and spaceflight. *P*-values based on two-tailed Student's *t*-test assuming equal variances, bed rest (BR) versus spaceflight (SF); SF subjects are 23 US astronauts from Mir and ISS spaceflights; BR subjects are 13 controls from NASA Johnson Space Center Flight Analog bed rest studies [51]

compression garment called a "Pingvin suit" [58]. Despite its widespread use, there is no published evidence that the "Pingvin suit" is effective in preventing musculoskeletal changes during spaceflight.

The first use of exercise by the US space program was the bungee exerciser device flown on early Gemini missions, primarily to provide an exercise stimulus that would allow cardiovascular responses to be examined [59]. Exercise countermeasures were not conducted during Apollo missions and were first introduced by NASA during the Skylab program (1973–1979). The modalities included a Mini-Gym exerciser (a rope and pulley device) and a Teflon plate on which in-place stepping to simulate walking and running could be conducted [60]. Calcium balance experiments conducted on Skylab 4 indicated that significant bone loss was occurring despite the countermeasures [61, 62].

In the era of short-duration US flights on the Space Shuttle, exercise during the missions was not mandatory, partly because of the desire to maximize time available for the performance of experimental payload tasks. However, a stowable passive treadmill known as the "Thornton treadmill" (after its developer William Thornton, a physician-astronaut [63]) was flown on many Shuttle missions. No controlled experiments were conducted to determine if exercise on this device was beneficial to bone.

Long-duration US presence on the International Space Station (ISS) provided the opportunity to study the efficacy of exercise countermeasures since each crew member was required to participate in a supervised exercise program. There is a widespread misconception that US astronauts exercise for up to 2.5 h per day during their time on orbit, but quantitative measurements have shown this not to be the case [6] since set-up and tear-down activities consume almost 60% of assigned time.

The exercise modalities available to US crew members during missions to the ISS up to and including Increment 16 (2008) were an interim resistance exercise device (iRED [64]); a free floating motorized treadmill (TVIS [65]) that could be used in active or passive mode; and a vibration isolated cycle ergometer (CVIS). Crew members kept careful logs of their exercise bouts on these devices [66], and foot forces measurements during exercise in four crew members [6] confirmed that low harness forces resulted in foot forces that were substantially below those found in similar activities on earth. This no doubt contributed to the lack of efficacy of these countermeasures in preventing bone loss [31].

Many questions remain unanswered regarding the optimal prescription of exercise countermeasures to prevent bone loss. The most important of these is whether or not a single "bolus" of exercise of any intensity can replace a full day of intermittent loading such as occurs on earth. An additional critical issue is the interaction of concomitant changes in bone and muscle—since the integrity of the two systems are intimately connected. The fact that exercise countermeasures have been unsuccessful to date does not mean that they might not be successful in the future once personalized, high load exercise of adequate duration is performed. There is one case study of impact loading that appears to have been successful in the calcaneus of a single crew member [67].

Based on publicly available information, it appears that no pharmacotherapeutic interventions have yet been conducted [68]. This is despite the fact that bisphosphonates have been shown to be effective in a bed rest setting [69].

## Knowledge Gaps

Because of the many difficulties of conducting research in space, knowledge of changes to the skeleton and of appropriate countermeasures has and will be plagued with limitations. However, as the space program embarks on longer duration missions, the occupational risks of space travel need to be defined if appropriate countermeasures are to be developed. In terms of the risk for early onset osteoporosis, the following is a list of open issues that need to be addressed in order to characterize the skeletal adaptation to the mechanical unloading of spaceflight:

- The factors or mechanisms that contribute to the variability in losses of BMD with spaceflight have yet to be identified. In particular, the roles of stress, hormonal changes and/or genetics remain to be elucidated [56].
- The impact on whole bone strength is not fully known. Crew member deficits in areal BMD as measured by

DXA do not reflect changes in "bone quality" or forces actually induced on bone during high physical load activity. There is a need for non-invasive assessments of indices known to influence whole bone strength such as whole bone geometry, cortical bone thickness, or cancellous bone microarchitecture, as well as a method to determine force loads on bone.

- Extensive longitudinal measures over the lifetime of crew members need to be conducted to monitor the effects of spaceflight and of recovery. Cross-sectional comparisons, such as those conducted with the ageing population, are limited in their ability to define patterns of lifetime bone loss for different sites and would not provide meaningful information for the management of astronaut long-term health.
- The impact of spaceflight on balance, coupling, and rate of remodeling has not been quantified at the level of the bone remodeling unit; neither have the impacts on cell function and number yet been quantified.
- QCT technology does not have the resolution to assess how loss of volumetric BMD in the trabecular compartment affects the microarchitecture. The time course and the impact of spaceflight-induced losses on trabecular microarchitecture (i.e., trabecular thinning or loss of trabecular connectivity) are unknown.
- The timing, extent, and variability of volumetric BMD recovery in bone compartments are still not established.
- The impact of multiple long-duration flights on bone loss and recovery, and on cortical bone thinning and subsequent periosteal expansion, is not known.
- Sex-based differences in bone loss during spaceflight have not been fully evaluated.
- The multiple factors that influence the variable rates of BMD recovery between individuals after spaceflight have not been assessed.
- The efficacy of anti-resorptive agents under weightless conditions of spaceflight has not been validated.
- The efficacy of exercise or nutritional countermeasures have not been fully investigated or validated.
- Estimations of whole bone strength for other skeletal sites (arm, wrist, spine) with a large number of crew member subjects need to be performed.

## Summary and Conclusion

The skeletal system of crew members adapts to the gravity unloading by reducing its mineral mass through increased bone resorption and uncoupled bone formation. The averaged monthly loss in BMD during a typical 6-month mission in low Earth orbit is 1–2% of pre-flight areal BMD (range 6–20% loss per 6 months of spaceflight). The changes in BMD are site-specific, and geometrical changes in the proximal femur have been associated with decrements in hip strength. There is evidence for greater loss in the trabecular compared to cortical compartment. The time course for the loss and recovery of bone mass during periods in space and back on Earth, and with various gravity levels, has not been determined nor completely characterized. It is necessary to expand skeletal measures and to characterize the response of the skeleton to the various levels of loading potentially encountered during exploration missions in order to manage any associated skeletal health risks by mitigation or treatment. Countermeasures used to date have not adequately loaded the skeleton to 1G levels.

Substantiating whether spaceflight increases the risk for accelerated osteoporosis ultimately centers on determining if spaceflight-induced skeletal changes are irreversible after return to Earth. If spaceflight-induced bone loss is not restored and decrements in whole bone strength are not recovered in the post-flight period, then crew members will experience the combined effects of space and of ageing on the skeleton and be predisposed to an earlier incidence of osteoporosis and fragility fractures. This risk will be even greater for female crew members since bone loss with spaceflight may be compounded by bone loss with menopause.

What determines if bone loss and whole bone strength are restored? Pre-flight and post-flight measurements of bone should include bone size and geometry, volumetric BMD of bone compartments, bone microarchitecture, and mechanical strength testing by computer modeling and virtual loading, as developed with these expanded measurements. Additionally, longitudinal measures during the post-career lifetime of a crew member should be conducted. Moreover, the time course of bone turnover during spaceflight will improve the ability to evaluate the risk of longer exposures to skeletal integrity and its impact on recovery back on Earth. These additional indices will enhance the probabilistic risk assessments for crew members returning from long duration spaceflight missions.

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